On Triazoles XLVIII [1]. Synthesis of Isomeric Amino-thiazolo-[1,2,4]triazole, Amino-[1,2,4]triazolo-[1,3]thiazine and -[1,3]thiazepine Derivatives

Ibolya Prauda and József Reiter

Egis Pharmaceuticals Ltd., P. O. Box 100, H-1475 Budapest, Hungary

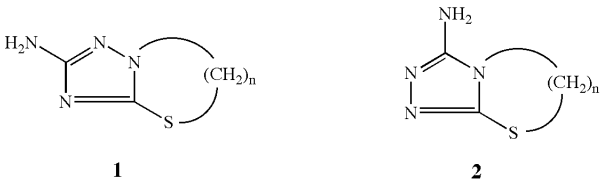
Received May 27, 2003

Isomeric type **1** and **2** amino-1,2,4-triazoles condensed with thiazole, thiazine and thiazepine rings were synthesised from 5-amino-2,3-dihydro-1*H*-1,2,4-triazol-3-thione and α,ω-dihaloalkanes through the 5-amino-3-(ω-haloalkylthio)-1*H*-1,2,4-triazole intermediates. The reaction conditions leading to derivatives **1** and **2**, respectively, were determined. A general and safe method for the unambiguous differentiation between structures **1** and **2** was offered by their cmr spectra.

J. Heterocyclic Chem., **40**, 821 (2003).

The preparative structure proof of some isoquinolinium salts, prepared recently [2], required isomeric type **1** and **2** amino-1,2,4-triazoles condensed with thiazole, thiazine and thiazepine rings (Scheme 1).

Scheme 1

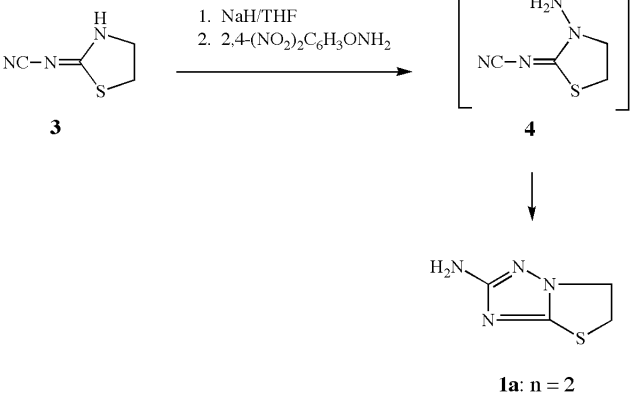


1 **2**

a: n = 2
b: n = 3
c: n = 4

Among the above compounds only the 2-amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**1a**, n = 2) was known [3], which had been prepared through a structure-proving synthesis from the sodium salt of 2-(cyanoimino)-thiazolidine (**3**) and *O*-(2,4-dinitrophenyl)hydroxylamine, through intermediate **4** in tetrahydrofurane at room temperature (Scheme 2). However, we needed a general method allowing the synthesis of all type **1** and **2** isomers.

Scheme 2

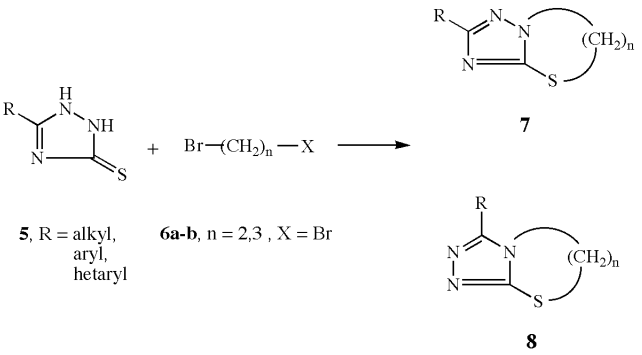


3 **4**

1a: n = 2

Different authors described the alkylation of a wide range of 5-alkyl- [4], 5-aryl- [5-11] and 5-hetaryl- [12-16] -2,3-dihydro-1*H*-1,2,4-triazol-5-thiones (**5**) [17] with dibromoalkanes **6a-b** (n = 2,3, X = Br) to yield type **7** or **8** (n = 2,3) condensed ring derivatives analogous to those of derivatives **1** and **2** to be synthesised (Scheme 3). However, the structure of the compounds obtained except those described by Sasaki *et al.* [8] and Ali *et al.* [11] is highly ambiguous, as the reaction conditions used by authors predict a different ring-fusion (see later) and the ring-fusion of compounds reported was not corroborated in any way.

Scheme 3

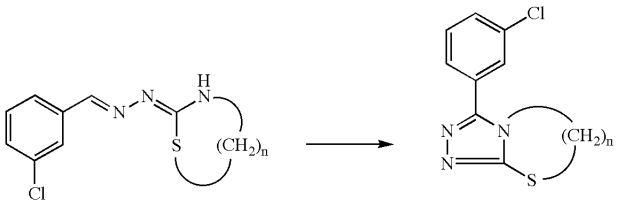


5, R = alkyl, aryl, hetaryl **6a-b**, n = 2,3 , X = Br

7 **8**

Ali and coworkers [11] used for the ring closure of **5** (R = 3-chlorophenyl) with 1,2-dibromoethane (**6a**, n = 2, X = Br) and 1,3-dibromopropane (**6b**, n = 3, X = Br) 1 mole of sodium methoxide in methanol and obtained after radial tlc separation the corresponding type **7** and **8** derivatives in 10 and 5 %, and 22 and 13 % yield, respectively. The structure of derivatives **8** was evident because they were identical with those obtained by oxidative ring closure of the corresponding thiazolidin-2-one and tetrahydro-2*H*-1,3-thiazin-2-one [(3-chlorophenyl)methylidene]-hydrazones (**9** and **10**, n = 2 and 3, respectively, Scheme 4). Consequently structure **7** should be ordered to their isomers obtained. Authors also listed the cmr peaks of derivatives **7** and **8**, but gave no assignment to them.

Scheme 4



9, n = 2
10, n = 3

8, Ar = 3-Cl-phenyl
n = 2,3

To elaborate a useful method for the synthesis of type **1** and **2** (n = 2-4) isomers we decided to study the reaction of 5-amino-2,3-dihydro-1*H*-1,2,4-triazol-3-thione (**11**) [18] with α,ω-dihaloalkanes (**6a-d**)(Scheme 5). Careful study of the reaction conditions showed that, when carried out it in mild condition (*e.g.* in cold methanol using 1 mole of sodium methoxide), the intermediate 5-amino-3-(ω-haloalkylthio)-1*H*-1,2,4-triazoles (**12a-d**, X = Br or Cl, n = 2-4) could be isolated, which on heating either alone or in solution in absence of base were changed to type **2** hydrohalides. However, when the ring closure is initiated with a further mole (or excess) of sodium methoxide or hydroxide or the reaction of **11** with **6a-c** is performed at room temperature in alcoholic solution and excess sodium methoxide type **1** (n = 2-4) derivatives are formed as main products (Scheme 5). This is in agreement with our previous results [19], namely, that when the anions formed from 5-amino-3-alkylthio-1*H*-1,2,4-triazoles were *N*-alkylated with different alkyl halides the main products were the 1-*N*-alkyl-derivatives formed in approximately 60 % yield, and the 2-*N*-alkyl-derivatives which were formed in approximately 35 % yield, while the 4-*N*-alkyl-derivatives were obtained in an amount of 4-5 % only. As the ring closure of anions formed from derivatives **12a-d** (n = 2-4) may proceed toward the triazole nitrogens 2 or 4 only, in basic conditions the formation of type **1** (n = 2-4) derivatives are to be expected as main products.

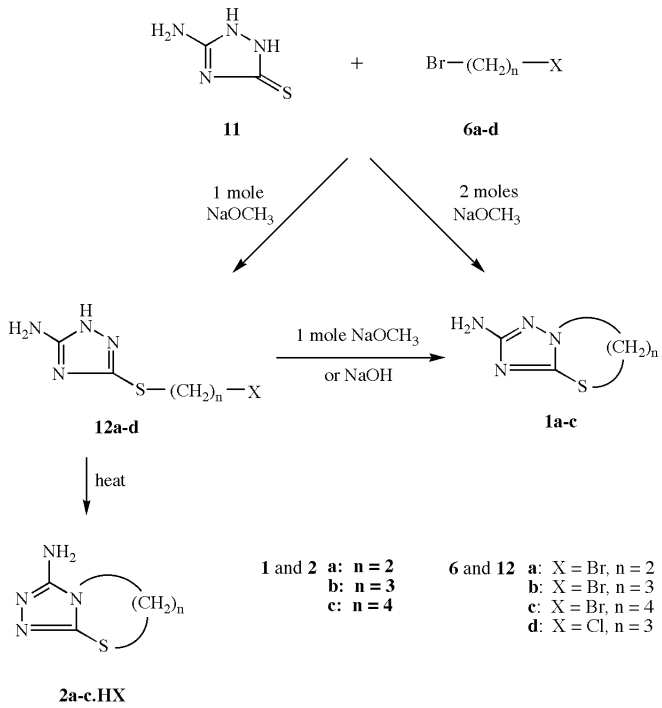
On the other hand, when the ring closure of derivatives **12a-d** (n = 2-4, X = Br, Cl) either isolated previously or formed *in situ* from the corresponding 1,2,4-triazole-thione, α,ω-dihaloalkane and 1 mole of base is provided in the absence of a further molecule of base the hydrogen halide liberated during the ring closure is trapped by the hydrazine moiety of the triazole ring making the most basic the triazole nitrogen 4, consequently causing preferably the formation of type **2** derivatives.

Taking in account the above facts in all those previous papers [4-5,7,9-10,12-13] in which the reactions of 1,2,4-triazole-thiones and α,ω-dihaloalkanes were performed without base had to prepare type **8** derivatives and not those of type **7** reported, and in that of paper [16] where the above reaction was carried out in a huge excess of potassium hydroxide type **7** derivatives had to be formed and not those of type **8** reported. It should be noted that type **7** structure of derivatives reported in [5] was just querried by Sasaki [8], too.

The 1*H* dominant tautomeric structure of derivatives **12a-d** (n = 2-4, X = Br, Cl) in DMSO-d_6 solution is consistent with the pmr spectra recorded. The chemical shift of the NH_2 groups appearing at δ = 6.1, 6.0, 6.0 and 6.05 ppm, respectively, even not excluding the 4*H* tautomeric structure points rather to their 1*H* dominant tautomeric structure in agreement with the previous results obtained with the 5-amino-3-alkylthio-1,2,4-triazoles [21] (Scheme 6) and corroborated also by ^{15}N-nmr [22].

Derivatives **1** and **2** could be easily differentiated by tlc, as their retention's were approximately 0.5 and 0.1-0.2,

Scheme 5



11

6a-d

1 mole $NaOCH_3$

2 moles $NaOCH_3$

12a-d

1 mole $NaOCH_3$ or NaOH

1a-c

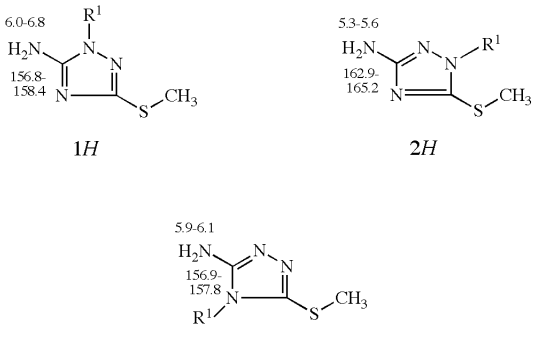
heat

2a-c.HX

1 and **2** **a**: **n = 2**
b: **n = 3**
c: **n = 4**

6 and **12** **a**: X = Br, n = 2
b: X = Br, n = 3
c: X = Br, n = 4
d: X = Cl, n = 3

Scheme 6



1*H*

2*H*

4*H*

respectively. However, a safe spectral proof of their structure was required.

Comparing the uv spectra of isomeric pairs **1a** – **2a**, **1b** – **2b** and **1c** – **2c**, respectively, taken in ethanolic, acidic (10 % ethanol + 90 % 0.1 *N* hydrochloric acid) and basic (10 % ethanol + 90 % 0.1 *N* sodium hydroxide) solutions in all cases a well detectable bathochromic shift of the maxima of derivatives **1** as compared with those of derivatives **2** was observed. However, no general rule could be formulated to order any maxima to type **1** or **2** structures.

The chemical shift of the amino groups of derivatives **1** and **2** taken in DMSO-d_6 solution significantly differed appearing between 5.18 and 5.37, and 5.72 and 5.92 ppm, respectively, in good agreement with those of 2- and 4-alkylated 5-amino-3-alkylthio-1,2,4-triazoles (Scheme 6) reported previously [20] giving an evidence of their structure.

However, a general and safe method for the differentiation between structures **1** and **2** offered only the cmr spectra, where the triazole carbon atoms bearing the amino group appeared in case of derivatives **1a-c** at 168.8, 162.6 and 162.3 ppm, respectively, while those of derivatives **2a-c** appeared at 153.1, 155.2 and 155.9 ppm, respectively. This is in full analogy with those of the corresponding carbon atoms of the 2- and 4-alkylated 5-amino-3-alkylthio-1,2,4-triazoles (Scheme 6) reported previously [20].

Derivatives **1c** (n = 4) and **2c** (n = 4) represent two new ring systems.

EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The ultraviolet spectra were obtained by a Varian Cary 1E UV-VIS instrument. The ms spectra were recorded on a Micromass LCT and a VG Trio 1000 instrument using direct inlet probe in EI mode as well as on a VG Quattro instrument (ES). The pmr and cmr measurements were performed using Varian Gemini-2000 and Varian Unity Inova 400 (400 MHz) instruments. Standard Varian HSQC and HMBC programs were used. As adsorbent of chromatographies Kieselgel 60 H (Merck 7736 for thin layer chromatography), as eluents different mixtures of petroleum ether, chloroform and methanol were used. Thin layer chromatographies were performed on 25 DC-Alufolien Kieselgel 60 F_{254} plates (Merck) with a 3:1 mixture of chloroform and methanol as eluent. The spots were detected by uv.

5-Amino-3-(2-bromoethyl)thio-1*H*-1,2,4-triazole (**12a**).

A mixture of 1.10 g (0.02 mole) of sodium methoxide, 2.32 g (0.02 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18], 25 ml of methanol, and 30.06 g (14 ml, 0.16 mole) of 1,2-dibromoethane (Fluka) was stirred at room temperature for 3.5 hours. The reaction mixture obtained was evaporated *in vacuo* to dryness and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents different mixtures of petroleum ether, chloroform and methanol of continuously increasing polarities were used. After evaporating the solvents from the appropriate fractions *in vacuo*, the crystalline residue was triturated with 5 ml of 2-propanol and filtered to yield 2.28 g (51%) of 5-amino-3-(2-bromoethyl)thio-1*H*-1,2,4-triazole (**12a**), mp 106-112° decomposed; pmr (DMSO-d_6): δ, ppm 3.38 [dt (J = 2.1 and 4.2 Hz), 2H, SCH_2], 3.71 [dt (J = 2.1 and 4.3 Hz), 2H, $BrCH_2$], 6.1 (bs, 2H, NH_2], 12.0 (b, 1H, NH); cmr (DMSO-d_6): decomposed during recording.

Anal. Calcd. for $C_4H_7BrN_4S$ (MW 223.10): C, 21.54; H, 3.16; Br, 35.82; N, 25.11; S, 14.37. Found: C, 21.38; H, 3.25; Br, 35.77; N, 25.23; S, 14.35.

5-Amino-3-(3-bromopropyl)thio-1*H*-1,2,4-triazole (**12b**).

A mixture of 1.78 g (0.033 mole) of sodium methoxide, 3.48 g (0.03 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18], 30 ml of methanol, and 18.18 g (9.2 ml, 0.09 mole) of 1,3-dibromopropane (Fluka) was stirred at room temperature for 1.5 hours. The mixture obtained was evaporated *in vacuo* to dryness and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents different mixtures of petroleum ether, chloroform and methanol of continuously increasing polarities were used. After evaporating the solvents from the appropriate fractions *in vacuo* the crystalline residue was triturated with 15 ml of ethyl acetate and filtered to yield 4.93 g (69 %) of 5-amino-3-(3-bromopropyl)thio-1*H*-1,2,4-triazole (**12b**), mp 63-67° decomposed; pmr (DMSO-d_6): δ, ppm 2.15 [qi (J = 6.8 Hz), 2H, CCH_2C], 3.05 [t (J = 6.9 Hz), 2H, SCH_2], 3.59 [t (J = 6.6 Hz), 2H, $BrCH_2$], 6.0 (bs, 2H, NH_2], NH not detected; cmr (DMSO-d_6): decomposed during recording.

Anal. Calcd. For $C_5H_9BrN_4S$ (MW 237.12): C, 25.33; H, 3.83; Br, 33.70; N, 23.63; S, 13.52. Found: C, 25.30; H, 3.99; Br, 33.77; N, 23.55; S, 13.60.

5-Amino-3-(4-bromobutyl)thio-1*H*-1,2,4-triazole (**12c**).

A mixture of 11.62 g (0.1 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18], 200 ml of methanol, 5.4 g (0.1 mole) of sodium methoxide and 172.74 g (95 ml, 0.8 mole) of 1,4-dibromobutane (Fluka) was stirred at room temperature for 1.5 hours. The mixture obtained was evaporated *in vacuo* to dryness and the residue was partitioned between 100 ml of water and 100 ml of dichloromethane. The phases were separated, the organic layer was dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was triturated with ether and filtered to yield 23.4 g (93 %) of 5-amino-3-(4-bromobutyl)thio-1*H*-1,2,4-triazole (**12c**), mp 99-102° decomposed. An analytical sample was recrystallised from ethyl acetate, mp 102-104° dec.; pmr (DMSO-d_6): δ, ppm 1.73 (m, 2H, CH_2-3'), 1.89 (m, 2H, CH_2-2'), 2.98 [t (J = 6.9 Hz), 2H, SCH_2], 3.54 [t (J = 6.5 Hz), 2H, $BrCH_2$], 6.0 (bs, 2H, NH_2], 12.0 (b, 1H, NH); cmr (DMSO-d_6): decomposed during recording.

Anal. Calcd. For $C_6H_{11}BrN_4S$ (MW 251.15): C, 28.69; H, 4.41; Br, 31.82; N, 22.31; S, 12.77. Found: C, 28.71; H, 4.50; Br, 31,69; N, 22.28; S, 12.80.

5-Amino-3-(3-chloropropyl)thio-1*H*-1,2,4-triazole (**12d**).

A mixture of 0.54 g (0.01 mole) of sodium methoxide, 1.16 g (0.01 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18], 10 ml of methanol, and 7.87 g (4.95 ml, 0.05 mole) of 1-bromo-3-chloropropane (Fluka) was stirred at room temperature for 24 hours. The reaction mixture obtained was evaporated

in vacuo to dryness and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents different mixtures of diethylether, chloroform and methanol of continuously increasing polarities were used. After evaporating the solvents from the appropriate fractions *in vacuo* the crystalline residue was triturated with 10 ml of diethylether and filtered to yield 1.33 g (69 %) of 5-amino-3-(3-chloropropyl)thio-1*H*-1,2,4-triazole (**12d**), mp 93-96° decomposed; pmr (DMSO-d_6): δ, ppm 1.99 [qi (J = 6.8 Hz), 2H, CCH_2C], 3.02 [t (J = 6.8 Hz), 2H, SCH_2], 3.72 [t (J = 6.3 Hz), 2H, $ClCH_2$], 6.05 (bs, 2H, NH_2), 12.0 (b, 1H, NH); cmr (DMSO-d_6): decomposed during recording.

Anal. Calcd. For $C_5H_9ClN_4S$ (MW 192.67): C, 31.17; H, 4.71; Cl, 18.40; N, 29.08; S, 16.64. Found: C, 31.26; H, 4.88; Cl, 18.44; N, 28.96; S, 16.50.

3-Amino-5,6-dihydro-thiazolo[2,3-*c*][1,2,4]triazole Hydrobromide (**2a.HBr**).

A solution of 1.12 g (0.005 mole) of 5-amino-3-(2-bromoethyl)thio-1*H*-1,2,4-triazole (**12a**) in 5 ml of dimethylformamide was stirred at 50° for 3.5 hours. The reaction mixture was evaporated *in vacuo* to dryness. The crystalline residue was triturated with 10 ml of 2-propanol and filtered to yield 0.95 g (85 %) of 3-amino-5,6-dihydro-thiazolo[2,3-*c*][1,2,4]triazole hydrobromide (**2a.HBr**), mp 251-255°; pmr (DMSO-d_6): δ, ppm 4.04 [dd (J = 6.1 and 6.4 Hz), 2H, CH_2-6], 4.92 [dd (J = 6.1 and 6.4 Hz), 2H, CH_2-5], 8.52 (bs, 2H, NH_2], 13.4 (b, 1H, NH); cmr (DMSO-d_6): δ, ppm 37.5 (C-6), 44.5 (C-5), 149.1 (C-3), 154.8 (C-7a).

Anal. Calcd. For $C_4H_7BrN_4S$ (MW 223.10): C, 21.54; H, 3.16; Br, 35.82; N, 25.11; S, 14.37. Found: C, 21.60; H, 3.30; Br, 35.77; N, 25.02; S, 14.40.

An analytical sample was partitioned between chloroform and water, the mixture made alkaline with 1 *N* sodium hydroxide, the phases were separated, the chloroform layer was washed with water, dried over anhydrous sodium sulphate, filtered, and evaporated *in vacuo* to dryness. The residue was recrystallised from ethyl acetate to yield 3-amino-5,6-dihydro-thiazolo[2,3-c][1,2,4]triazole (**2a**) base, mp 240-244°; R_f = 0.08; pmr (DMSO-d_6): δ, ppm 3.91 [t (J = 6.2 Hz), 2H, CH_2-6], 3.98 [t (J = 6.2 Hz), 2H, CH_2-5], 5.89 (bs, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 39.3 (C-6), 42.3 (C-5), 151.4 (C-7a), 153.1 (C-3); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 229sh (3.1), 218 (4.8); uv (10 % EtOH + 90 % 0.1 *N* hydrochloric acid): λ_{max} ($\varepsilon.10^{-3}$) = 247sh (1.4), 217 (7.5); uv (10 % EtOH + 90 % 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon.10^{-3}$) = no maximum observed.

Anal. Calcd. For $C_4H_6N_4S$ (MW 142.18): C, 33.79; H, 4.25; N, 39.40; S, 22.55. Found: C, 33.72; H, 4.30; N, 39.32; S, 22.50.

2-Amino-5,6-dihydro-thiazolo[3,2-*b*][1,2,4]triazole (**1a**).

Method A.

To a mixture of 2.16 g (0.04 mole) of sodium methoxide 2.32 g (0.02 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18] and 25 ml of methanol 11.27 g (5.2 ml, 0.06 mole) of 1,2-dibromoethane (Fluka) was added with stirring at 0°. The reaction mixture was allowed to warm to room temperature, and stirred for 60 hours. The methanol was evaporated *in vacuo* to dryness, and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents, different mixtures of petroleum ether, chloroform and methanol of continuously increasing polarities were used. The appropriate fractions were evaporated *in vacuo* to dryness to yield 1.24 g (43 %) of 2-amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole (**1a**) as a crystalline product, that was recrystallised first from a mixture of 9 ml of ethyl acetate and 1 ml of acetonitrile; mp 142-146°, then from benzene, mp 150-153°, Lit [3] mp 156-157° (benzene); R_f = 0.47; pmr (DMSO-d_6): δ, ppm 3.85 [dt (J = 7.0 and 1.2 Hz), 2H, CH_2-6], 4.06 [dt (J = 7.0 and 1.2 Hz), 2H, CH_2-5], 5.37 (bs, 2H, NH_2], Lit [3] pmr (deuteriochloroform): δ, ppm 3.81 (t, 2H, J = 7.0 Hz), 3.90 (bs, 2H), 4.18 (t , 2H, J = 7 Hz); cmr (DMSO-d_6): δ, ppm 33.0 (C-6), 46.5 (C-5), 156.2 (C-7a), 168.8 (C-2); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 238 (3.2); uv (10 % EtOH + 90 % 0.1 *N* hydrochloric acid): λ_{max} ($\varepsilon.10^{-3}$) = 247 (4.8); uv (10 % EtOH + 90 % 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon.10^{-3}$) = no maximum observed.

Anal. Calcd. For $C_4H_6N_4S$ (MW 142.18): C, 33.79; H, 4.25; N, 39.40; S, 22.55. Found: C, 33.69; H, 4.41; N, 39.31; S, 22.67.

Method B.

A mixture of 0.54 g (0.01 mole) of sodium methoxide and 1.12 g (0.005 mole) of 5-amino-3-(2-bromoethyl)thio-1*H*-1,2,4-triazole (**12a**) in 5 ml of methanol was stirred at room temperature for 12 hours. The methanol was evaporated *in vacuo* to dryness, and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents, different mixtures of petroleum ether and dichloromethane of continuously increasing polarities were used. The appropriate fractions were evaporated *in vacuo* to dryness to obtain 0.29 g (41 %) of 2-amino-5,6-dihydrothiazolo-[3,2-*b*][1,2,4]triazole (**1a**) as a crystalline product, that was recrystallised from benzene, mp 151-153°; its spectral data were identical with those of **1a** prepared by Method A.

3-Amino-5,6-dihydro-7*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine Hydrobromide (**2b.HBr**).

A solution of 0.92 g (0.0039 mole) of 5-amino-3-(3-bromopropyl)thio-1*H*-1,2,4-triazole (**12b**) in 4 ml of dimethylformamide was stirred at 60° for 4 hours. The reaction mixture was evaporated *in vacuo* to dryness The crystalline residue was triturated with 10 ml of 2-propanol and filtered to yield 0.40 g (43 %) of 3-amino-5,6-dihydro-7*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine hydrobromide (**2b.HBr**), mp 192-195°; pmr (DMSO-d_6): δ, ppm 2.29 (m, 2H, CCH_2C), 3.24 (m, 2H, SCH_2), 3.90 (m, 2H, NCH_2), 8.33 (bs, 2H, NH_2), 13.4 (b, 1H, NH); cmr (DMSO-d_6): δ, ppm 21.9 (C-6), 24.1 (C-7), 42.5 (C-5), 143.5 (C-8a), 150.8 (C-3).

Anal. Calcd. for $C_5H_9BrN_4S$ (MW 237.12): C, 25.33; H, 3.83; Br, 33.70; N, 23.63; S, 13.52. Found: C, 25.40; H, 4.02; Br, 33.58; N, 23.71; S, 13,48.

An analytical sample was partitioned between chloroform and water, the mixture made alkaline with 1 *N* sodium hydroxide, the phases were separated, the chloroform layer washed with water, dried over anhydrous sodium sulphate, filtered, and evaporated *in vacuo* to dryness. The residue was recrystallised from ethyl acetate to yield 3-amino-5,6-dihydro-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3]thiazine (**2b**) base, mp 255-260°; R_f = 0.11; pmr (DMSO-d_6): δ, ppm 2.18 (m, 2H, CH_2-6), 3.06 [t (J = 3.9 Hz), 2H, CH_2-7], 3.72 [t (J = 6.1 Hz), 2H, CH_2-5], 5.72 (s, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 23.3 (C-7), 24.3 (C-8), 41.4 (C-6), 138.5 (C-8a), 155.2 (C-3); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 226 (6.9); uv (10 % EtOH + 90 % 0.1 *N* hydrochloric acid): λ_{max} ($\varepsilon.10^{-3}$) = 239 (3.6); uv (10 % EtOH + 90 % 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon.10^{-3}$) = no maximum observed.

Anal. Calcd. For $C_5H_8N_4S$ (MW 156.21): C, 38.45; H, 5.16; N, 35.87; S, 20.53. Found: C, 38.55; H, 5.33; N, 35.77; S, 20.48.

2-Amino-5,6-dihydro-7*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazine (**1b**).

Method A.

To a mixture of 2.16 g (0.04 mole) of sodium methoxide, 2.32 g (0.02 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18] and 25 ml of methanol 12.11 g (6.1 ml, 0.06 mole) of 1,3-dibromopropane (Fluka) was added with stirring at 0°. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The methanol was evaporated *in vacuo* to dryness, and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents, different mixtures of petroleum ether, chloroform and methanol of continuously increasing polarities were used. After evaporating the solvents from the appropriate fractions *in vacuo*, the residue crystallised. It was triturated with a mixture of 9 ml of ethyl acetate and 1 ml of 2-propanol, and filtered to yield 1.47 g (47 %) of 2-amino-5,6-dihydro-7*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazine (**1b**) mp 132-135°. An analytical sample was recrystallised from ethyl acetate, mp 139-142°; R_f = 0.48; pmr (DMSO-d_6): δ, ppm 2.19 (m, 2H, CH_2-6), 3.18 [dt (J = 5.5 and 0.5 Hz), 2H, CH_2-5], 3.93 [t (J = 6.0 Hz), 2H, CH_2-7], 5.18 (bs, 2H, NH_2]; cmr (DMSO-d_6): δ, ppm 23.8 (C-6), 25.6 (C-5), 46.8 (C-7), 144.0 (C-8a), 162.7 (C-2); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 238 (3.6); uv (10 % EtOH + 90 % 0.1 *N* hydrochloric acid): λ_{max} ($\varepsilon.10^{-3}$) = 252 (4.2), 224 (5.8); uv (10 % EtOH + 90 % 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon.10^{-3}$) = no maximum observed.

Anal. Calcd. For $C_5H_8N_4S$ (MW 156.21): C, 38.45; H, 5.16; N, 35.87; S, 20.53. Found: C, 38.55; H, 5.33; N, 35.77; S, 20.48.

Method B.

A mixture of 0.12 g (0.003 mole) of sodium hydroxide and 0.71 g (0.003 mole) of 5-amino-3-(3-bromopropyl)thio-1*H*-1,2,4-triazole (**12b**) in 4 ml of methanol was stirred at room temperature for 3 hours. The methanol was evaporated *in vacuo* to dryness, and the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents, different mixtures of petroleum ether and methanol of continuously increasing polarities were used. After evaporating the solvents from the appropriate fractions *in vacuo* the residue crystallised. It was triturated with 5 ml of ethyl acetate to yield 0.31 g (66 %) of 2-amino-5,6-dihydro-7*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazine (**1b**), mp 138-141°.The product is identical (mixed mp, pmr) with that of **1b** obtained by Method A.

3-Amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[3,4-*b*][1,3]thiazepine Hydrobromide (**2c.HBr**).

A solution of 7.53 g (0.03 mole) of 5-amino-3-(4-bromobutyl)thio-1*H*-1,2,4-triazole (**12c**) in 30 ml of dimethylformamide was stirred at 120° for 30 minutes. The reaction mixture was evaporated *in vacuo* to dryness, the residue (7.46 g) was triturated with 50 ml of 2-propanol, filtered and washed with 2-propanol to yield 4.52 g (60 %) of 3-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[3,4-*b*][1,3]thiazepine hydrobromide (**2c.HBr**), mp 202-205°. pmr (DMSO-d_6): δ, ppm 1.79 (m, 2H, CH_2-6), 2.07 (m, 2H, CH_2-7), 2.96 (m, 2H, CH_2-8), 4.10 (m, 2H, CH_2-5), 8.42 (s, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 26.0 (C-7), 31.2 (C-6), 32.2 (C-8), 44.4 (C-5), 148.6 (C-9a), 151.4 (C-3).

Anal. Calcd. for $C_6H_{11}BrN_4S$ (MW 251.15): C, 28.69; H, 4.41; Br, 31.82; N, 22.31; S, 12.77. Found: C, 28.53; H, 4.61; Br, 31,64; N, 22.25; S, 12.73.

An analytical sample was partitioned between chloroform and water, the mixture was made alkaline with 1 *N* sodium hydroxide, the phases were separated, the chloroform layer was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was recrystallised from ethyl acetate to yield 3-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[3,4-*b*][1,3]thiazepine (**2c**) base, mp 263-266°. R_f = 0.23; pmr (DMSO-d_6): δ, ppm 1.65 [qi (J = 4.9 Hz), 2H, CH_2-6]), 2.03 [qi (J = 5.4 Hz), 2H, CH_2-7], 2.73 (m, 2H, CH_2-8), 3.89 (m, 2H, CH_2-5), 5.92 (bs, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 27.8 (C-7), 32.2 (C-6), 32.7 (C-8), 42.9 (C-5), 144.8 (C-9a), 156.1 (C-3); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 252 (7.2), 216sh (5.6); uv (10 % EtOH + 90 % 0.1 *N* hydrochloric acid): λ_{max} ($\varepsilon.10^{-3}$) = 247 (5.7), 208 (7.6); uv (10 % EtOH + 90 % 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon.10^{-3}$) = 249 (5.9).

Anal. Calcd. for $C_6H_{10}N_4S$ (MW 170.24): C, 42.33; H, 5.92; N, 32.91; S, 18.83. Found: C, 42.45; H, 6,12; N, 33.01; S, 18.66.

2-Amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepine (**1c**).

Method A.

To a mixture of 2.16 g (0.04 mole) of sodium methoxide 2.32 g (0.02 mole) of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**11**) [18] and 25 ml of methanol 12.96 g (7.1 ml, 0.06 mole) of 1,4-dibromobutane (Fluka) was added with stirring at 0°. The reaction mixture was allowed to warm to room temperature, and stirred for 1.5 hours. The methanol was evaporated *in vacuo* to dryness, the residue was dry-column flash chromatographed on Kieselgel 60 H. As eluents different mixtures of petroleum ether, chloroform and methanol of continuously increasing polarities were used. After evaporating the solvents *in vacuo*, the residue crystallised. It was triturated with a mixture of 9 ml of ethyl acetate and 1 ml of 2-propanol, and filtered to yield 1.47 g (43 %) of 2-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepine (**1c**) mp 165-179°. An analytical sample was recrystallised from ethyl acetate, mp 180-184°; R_f = 0.52; ms (EI): M^+ = 170; pmr (DMSO-d_6): δ, ppm 1.72 (m, 2H, CH_2-7), 2.04 (m, 2H, CH_2-6), 2.83 (m, 2H, CH_2-5), 4.06 (m, 2H, CH_2-8), 5.2 (bs, 2H, NH_2], cmr (DMSO-d_6): δ, ppm 26.3 (C-7), 31.5 (C-6), 31.7 (C-5), 49.9 (C-8), 148.4 (C-3a), 162.3 (C-2); uv (EtOH): λ_{max} ($\varepsilon.10^{-3}$) = 257 (4.0), 239 (3.0); uv (10 % EtOH + 90 % 0.1 *N* hydrochloric acid): λ_{max} ($\varepsilon.10^{-3}$) = 266 (6.0); uv (10 % EtOH + 90 % 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon.10^{-3}$) = 254 (4.5).

Anal. Calcd. for $C_6H_{10}N_4S$ (MW 170.24): C, 42.33; H, 5.92; N, 32.91; S, 18.83. Found: C, 42.31; H, 6,01; N, 32.88; S, 18.86.

Method B.

A mixture of 0.2 g (0.005 mole) of sodium hydroxide and 1.25 g (0.005 mole) of 5-amino-3-(4-bromobutyl)thio-1*H*-1,2,4-triazole (**12c**) in 5 ml of methanol was stirred at room temperature for 3 hours. The methanol was evaporated *in vacuo* to dryness and the residue was dry-column flash chromatographed on

Kieselgel 60 H. As eluents, different mixtures of petroleum ether, dichloromethane and methanol of continuously increasing polarities were used. After evaporating the solvents from the appropriate fractions *in vacuo* the residue crystallised. It was triturated with ethyl acetate and filtered to yield 0.32 g (38 %) of 2-amino-5,6,7,8-tetrahydro-[1,2,4]triazolo[5,1-*b*][1,3]thiazepine (**1c**), mp 178-182°. The product is identical (mixed mp, pmr) with that of **1c** obtained by Method A.

Acknowledgement.

The authors wish to express their thanks to dr. Sándorné Sólyom for recording the ir spectra, to dr. Éva Szabó and dr. Péter Slégel for recording the ms spectra, Mrs. Magdolna Nagy and dr. István Kövesdi for recording the nmr spectra, to Miss Zsófia Kárpáti for recording the uv spectra, to Mrs. Hirkóné Magdolna Csík for performing the elementar analysis and to Mrs. Lászlóné Berei and Mrs. Lászlóné Nyikos for technical help.

REFERENCES AND NOTES

[1] For Part XLVII see G. Berecz and J. Reiter, *J. Heterocyclic Chem.*, **40**, 813 (2003).

[2] I. Prauda, and J. Reiter, Part XLIX of this series, *J. Heterocyclic Chem.*, (submitted).

[3] Ch. Iwata, M. Watanabe, Sh. Okamoto, M. Fujimoto, M. Sakae, M. Katsurada and T. Imanishi, *Synthesis (Communications)*, **1988**, 261.

[4] A. Singh, R. N. Handa and H. K. Pujari., *Indian J. Chem. Sect. B*, **16**, 475 (1978).

[5] K. S. Dhaka, J. Mohan, V. K. Chadha and H. K. Pujari, *Indian J. Chem.*, **12**, 485 (1974).

[6] R. P. Gupta, M, L. Sachdeva and H. K. Pujari., *Indian J. Chem. Sect. B*, **15**, 746 (1977).

[7] K. K. Jain and J. K. Pujari, *Indian J. Chem. Sect. B*, **22**, 249 (1983).

[8] T. Sasaki, T. Ohno and E. Ito, *Chem. Pharm Bull.*, **32**, 5040 (1984).

[9] B. N. Goswami, J. C. S. Kataky and J. N. Baruah, *J. Heterocyclic Chem.*, **23**, 1439 (1986).

[10] R. Pal, R. Sharma, S. Kumar, R. Dahiya and H. K. Pujari, *Indian J. Chem. Sect. B*, **33**, 634 (1994).

[11] S. Ali., J. S. Eilkie and K. N. Winzenberg, *Aust. J. Chem.*, **50**, 911 (1997).

[12] P. C. Joshi and P. C. Joshi, *J. Indian Chem. Soc.*, **55**, 465 (1978).

[13] M. K. Pant, R. Durgapal, J. Rekha and C. Puran, *Indian J. Chem. Sect. B*, **22**, 712 (1983).

[14] Z. K. A. El-Samii and S. A. El-Feky, *Phosphorous, Sulfur Silicon Relat. Elem.*, **101**, 29 (1995).

[15] H. Foks, A. Czarnocka-Janowicz, W. Rudnicka, B. Damasiewicz and A. Nasal, *Acta Pol. Pharm.*, **52**, 415 (1995).

[16] Zh. Wang, H, Shi and H. Shi, *Synthetic Communications*, **31**, 2841 (2001).

[17] These compounds are described in different tautomeric structures. Their tautomeric structure shown on the slide was proved by our uv experiments see [2].

[18] F. Arndt and E. Milde, *Chem. Ber.*, **54**, 2110 (1921).

[19] J. Reiter, T. Somorai, P. Dvortsák and Gy. Bujtás, *J. Heterocyclic Chem.*, **22**, 385 (1985).

[20] P. Dvortsák, J. Reiter, T. Somorai and P. Sohár, *Magn. Res. Chem.*, **23**, 194 (1985).

[21] J. Reiter, T. Somorai, Gy. Jerkovich and P. Dvortsák, *J. Heterocyclic Chem.*, **19**, 1157 (1982).

[22] A. M. Orendt, J. Michl and J. Reiter, *Magn. Res. Chem.*, **27**, 1-3 (1989).